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Proposed Re-evaluation Decision PRVD2011-15

Denatonium Benzoate

(publié aussi en français)

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Overview

Proposed Re-evaluation Decision for Denatonium Benzoate

After a re-evaluation of the animal repellent denatonium benzoate, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of products containing denatonium benzoate for sale and use in Canada.

An evaluation of available scientific information found that products containing denatonium benzoate do not present unacceptable risks to human health or the environment when used according to label directions. No additional data are being requested at this time.

This proposal affects all end-use products containing denatonium benzoate registered in Canada. Once the final re-evaluation decision is made, the registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for denatonium benzoate and presents the reasons for the proposed re-evaluation decision. The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of denatonium benzoate.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[2] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration. The Act also requires that products have value[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern and rigorous risk assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a re-evaluation decision on denatonium benzoate, the PMRA will consider all comments received from the public in response to this consultation document.[4] The PMRA will then publish a Re-evaluation Decision[5] on denatonium benzoate, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this overview, please refer to the Science Evaluation of this consultation document.

What Is Denatonium Benzoate?

Denatonium benzoate is an animal repellent that is primarily used to control wild and domestic animals from feeding on trees, shrubs and other non-food woody plants. It acts as a bittering agent and deters animals such as deer from chewing on treated plants and outdoor household items due to its extremely bitter and unpleasant taste. In the end-use products, denatonium benzoate is formulated as a liquid solution or suspension which is applied via hand-held spray equipment.

Health Considerations

Can Approved Uses of Denatonium Benzoate Affect Human Health?

Denatonium Benzoate is unlikely to affect your health when used according to the label directions.

Exposure to denatonium benzoate may occur when applying the product or by entering treated sites. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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4 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

5 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. Denatonium benzoate was of moderate acute toxicity to laboratory animals exposed via the oral route, but is extremely bitter and unlikely to be ingested in any appreciable amount by humans. It was of low acute toxicity to animals exposed by either the inhalation or dermal route. Denatonium benzoate was not irritating to the eyes or skin and is not considered to be a skin sensitizer. The available data indicate that denatonium benzoate does not damage genetic material and does not represent a carcinogenic concern.

The available database was sufficient to conclude that there is a very low level of concern for the hazard following exposure to denatonium benzoate and a quantitative risk assessment was not required.

Residues in Water and Food

Dietary risks from food and water are not of concern.

There are no direct food or feed uses registered in the United States and Canada for denatonium benzoate. Dietary risk to humans is not likely to be of concern based on the registered use, low application rate, and bitterness of the compound.

Non-Occupational Risks From Denatonium Benzoate

Non-occupational risks are not of concern.

Dermal, inhalation and incidental oral exposure to denatonium benzoate in residential settings are not likely to be of concern when the product is used according to label directions.

Occupational Risks From Handling Denatonium Benzoate

Occupational risks are not of concern.

Occupational exposure to individuals loading, applying and performing postapplication activities are not likely to be of concern when the product is used according to label directions.

Precautionary and hygiene statements on the label (for example, wearing of personal protective equipment) are considered adequate to protect individuals from any unnecessary risk due to occupational exposure. Label statements are required to be standardized for all products to ensure consistency.

Environmental Considerations

What Happens When Denatonium Benzoate Is Introduced Into the Environment?

Denatonium Benzoate is not mobile and does not pose a potential risk to terrestrial and aquatic organisms.

Denatonium benzoate is used in Canada as a repellent, and it is applied to deter animals from feeding on treated plants. Denatonium benzoate is a soluble chemical which is not expected to volatilize. Phototransformation and hydrolysis are not significant routes of transformation. Biotransformation rates are unknown. However, biotransformation studies in soil and water were waived by PMRA with the rationale that there is negligible potential exposure to the environment. It is not mobile in soils and soil column leaching studies indicate that it is not expected to leach significantly in soil. The only known transformation product is lignocaine which was obtained during hydrolysis at low pH, but its fate in the environment has not been characterized.

When denatonium benzoate is used for repelling animals from plants, there is a very low potential that sensitive terrestrial and aquatic species will be exposed. In Canada, only pump sprayers (back pack, hand pump or mechanical pump sprayers) are allowed for its use which limits the exposure to small areas. The risk assessment with available data indicates that denatonium benzoate presents negligible risk to fish, amphibians and aquatic invertebrates. For birds, the risk from consuming food sources contaminated during application is expected to be negligible based on the limited use pattern. Birds are not expected to consume food sources (such as leaves or tree bark) that are directly sprayed with denatonium benzoate. Negligible risk is expected for mammals since denatonium benzoate has a very bitter taste and is applied as a repellent for mammals. There are no toxicity data available on terrestrial invertebrates, but based on the use pattern, the potential exposure is expected to be limited. Therefore, no additional data is required at this time.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

As a result of the re-evaluation of denatonium benzoate, the PMRA is proposing additional mitigation measures on the labels products to address the potential risks identified in this assessment.

Human Health

- A statement clarifying that the product is only for outdoor use.
- Standardize statements for personal protective equipment and restricted entry interval for all domestic product labels.

Environment

- Standard statements for avoiding drift and contamination of water supplies for all commercial product labels.

A submission to implement label revisions will be required within 90 days of finalization of the re-evaluation decision.

Next Steps

Before making a re-evaluation decision on denatonium benzoate, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision on denatonium benzoate, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

Science Evaluation

1.0 Introduction

Denatonium benzoate is an animal repellent that is used to control damage caused by wild and domestic animals to plants and outdoor household items. It deters animals from chewing and or feeding on treated plants and outdoor household items due to its extremely bitter taste. It does not have a pesticidal mode of action; therefore, it is considered as a non-conventional pesticide.

Denatonium benzoate meets the criteria for a non-conventional Pest Control Product as per the Regulatory Proposal PRO2010-06, *Guidelines for the Registration of Non-Conventional Pest Products* published in 2010 for the following reasons:

- The product is used in such a manner as to not result in significant human or environmental exposure. This criteria is met by the very low concentration used, quantity sold per annum and the overall quantity applied in the deterrence of nuisance animals. A further decrease in exposure is anticipated due to the infrequent and/or seasonal use of the products in Canada. Due to the extremely bitter taste of the compound, accidental ingestion by humans is considered very unlikely.

- The pesticidal action of the product is not the result of toxicity to the target organism. The product acts as a repellent following tasting of the extremely bitter compound and there are no other known pesticidal properties.

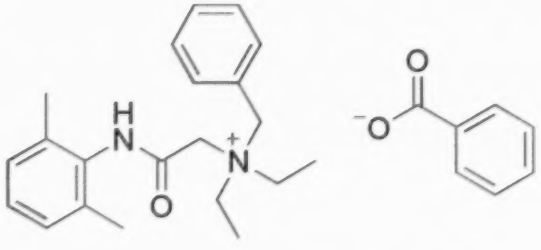
- The product is widely used in society as a commodity product with no known deleterious effects. It is used as a bittering agent in hazardous household products such as liquid detergent and anti-freeze to deter accidental ingestion. It is also added as an ingredient in anti-nail biting preparations.

Following the re-evaluation announcement for denatonium benzoate, the registrant of the technical grade active ingredient in Canada indicated that they intended to provide continued support for all uses included on the labels of commercial and domestic class end-use pest control products in Canada.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common Name	Denatonium Benzoate
Trade Name	Bitrex
Function	Repellent

Chemical Family	Benzoate
Chemical Name	
1 International Union of Pure and Applied Chemistry (IUPAC)	Benzyldiethyl [(2,6-xylylcarbamoyl)methyl] ammonium benzoate
2 Chemical Abstracts Service (CAS)	N-[2-[2,6-dimethyl phenyl)amino]-2-oxoethyl]-N,N- diethylbenzenemethanaminium benzoate
Chemical Class:	Quaternary ammonium salt
CAS Registry Number	3734-33-6
Molecular Formula	$C_{28}H_{34}N_2O_3$
Molecular Weight	446.59
Structural Formula	
Registration Number	25197
Purity of the Technical Grade Active Ingredient	99.9% NS (limits: 99.5 - 100%)

Identity of relevant impurities of human health or environmental concern:

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	< 1 × 10-7 mm Hg at 60°C
Ultraviolet (UV)/visible spectrum	Not expected to absorb at at $\lambda > 350$nm
Solubility in water at 25°C	4.5 g/100 mL
n-Octanol–water partition coefficient at 25 °C	pH = 6.5-7.5 log K_{ow} = - 4.1 × 10-2 K_{ow} =0.9098
Dissociation constant at 25°C	pK_a = 4.2

2.3 Description of Registered Denatonium Benzoate Uses

Denatonium benzoate is registered in Canada for use as an animal repellent. It is one of the most bitter substances known and is used as a taste repellent to deter animals. Denatonium benzoate is primarily used to prevent deer from feeding or gnawing on trees, shrubs and other non-food woody plants. Other registered uses include uses on outdoor household areas such as bushes, ornamental plants and flowers, siding, fences, posts, garbage containers, etc. Target pests also include various animals such as dogs, cats, rabbits, raccoons, beavers, mice, rats, squirrels, voles, porcupines, some types of granivorous birds, fruit eating birds and carrion crows. Currently registered in Canada, there is one technical, two commercial, and three domestic products containing denatonium benzoate. Appendix I list all products containing denatonium benzoate that are currently registered as of June 3, 2011 under the authority of the *Pest Control Products Act*.

Uses of denatonium benzoate belong to the following use-site categories: various indoor and outdoor sites on non-food and non-feed areas. Denatonium benzoate is formulated as a liquid solution or suspension and is applied via hand-held sprayers. Applications are usually made in spring and fall as necessary.

3.0 Impact on Human Health and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels where no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species.

3.1 Toxicology Summary

The available toxicology data are limited to some acute toxicity studies, genotoxicity studies and a limited chronic/ carcinogenicity assay conducted in rats.

Denatonium benzoate was of moderate acute toxicity to laboratory animals exposed via the oral route, but is extremely bitter and unlikely to be ingested in any appreciable amount by humans. It was of low acute toxicity to animals exposed by either the inhalation or dermal route. Denatonium benzoate was not irritating to the eyes or skin of rabbits and did not cause skin sensitization in guinea pigs.

One supplemental chronic/carcinogenicity study conducted using rats is available. In this study, rats were fed up to 16 mg/kg bw/day of denatonium benzoate via gavage daily for two years. There were no effects on the health of the animals observed (including following ophthalmological, hematological and pathological examination). Results from both an in vitro bacterial mutation assay and an in vivo mouse micronucleus assay were negative and indicate that denatonium benzoate is not genotoxic. The available data indicate that denatonium benzoate does not represent a carcinogenic concern.

The available database is considered sufficient to conclude that there is a very low level of concern for the hazard following exposure to denatonium benzoate and a quantitative risk assessment is not required.

3.2 Occupational and Non-Occupational Risk Assessment

3.2.1 Toxicology Endpoint Selection for Occupational Risk Assessment

Given that this active meets the criteria for a non-conventional Pest Control Product, a qualitative assessment of denatonium benzoate was conducted.

3.2.1.1 Dermal Absorption

In the absence of a specific dermal absorption study, dermal absorption was refined from 100% to 50% based on a weight-of-evidence approach using the physical-chemical properties. The dermal absorption of denatonium benzoate may be lower than 50%; however, further refinement is not possible without additional data.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to denatonium benzoate through loading or applying the pesticide, and when entering a treated site to conduct activities such as scouting. Exposure estimates due to mixing the product were not required as the product is ready-to-use. However, for most scenarios there were no data available for loading exposure, so mixing/loading unit exposure values were used instead. The resulting exposure estimates will likely overestimate exposure.

3.2.2.1 Loader and Applicator Exposure and Risk Assessment

Occupational exposure to denatonium benzoate is expected to be short-term and predominantly by the inhalation and dermal routes when workers are exposed during loading and application. Exposure was estimated based on a worker wearing the current label PPE (long-sleeved shirt, long pants and chemical resistant gloves), applying by backpack sprayer, and maximum

estimates of amount potentially handled in a day. The potential exposure to denatonium benzoate was very low (<3 µg/kg bw/day); yet this is considered to be an overestimate of exposure as mixing was included in the exposure estimate.

Risk to denatonium benzoate for loaders and applicators is not expected to be of concern due to the low toxicity of denatonium benzoate and low potential for exposure when label directions are followed. The PMRA requires an additional label statement, for all commercial products, clarifying that the product is for outdoor use only. Proposed label amendments are listed in Appendix II.

3.2.2.2 Postapplication Worker Exposure and Risk Assessment

Worker postapplication exposure following application of denatonium benzoate is expected to be negligible, given the sites and timing of application. Scouting may occur a few weeks to months following application; however, contact with treated foliage is expected to be minimal as damage would be readily apparent. Potential high-exposure activities, such as pruning may occur prior to application, as denatonium benzoate is non-systemic and would only protect those parts of the plant that have been sprayed. Current label instructions restrict entry into treated sites until spray has dried.

Risk to denatonium benzoate for workers entering treated sites is not expected to be of concern due to the low toxicity of denatonium benzoate and low potential for exposure when label directions are followed.

3.2.3 Non-Occupational Exposure and Risk Assessment

Residential risk assessment involves estimating risks to the general population, including children, during or after pesticide application.

Residential Applicator Exposure and Risk Assessment
Homeowners have the potential for short-term (1–30 days) exposure to denatonium benzoate during application to trees/shrubs and other outdoor areas to discourage damage from feeding animals. Inclusion of mixing and loading exposure was not required as the product is ready-to-use; however, for most scenarios there were no data available for application exposure, so mixing/loading/application unit exposure values were used instead. The resulting exposure estimates will likely overestimate exposure.

Exposure was estimated based on a homeowner wearing shorts and a short-sleeved shirt, maximum estimates of amount potentially handled in a day, and typical residential application equipment. The potential exposure to denatonium benzoate was very low (<3 µg/kg bw/day); yet this is considered to be an overestimate of exposure as mixing and loading were included in the exposure estimate.

Risk to denatonium benzoate for homeowners is not expected to be of concern due to the low toxicity of denatonium benzoate and low potential for exposure when label directions are followed. The PMRA requires an additional label statement, for all domestic products, clarifying that the product is for outdoor use only. In addition, standardize statements for personal protective equipment and restricted entry interval are required for all domestic product labels. Proposed label amendments are listed in Appendix II.

Postapplication Non-Occupational Exposure and Risk Assessment

Non-occupational postapplication exposure may occur from the use of denatonium benzoate in residential settings; however, exposure is expected to be minimal given the use scenario, timing of application and low likelihood of contact with sprayed areas. Current label instructions restrict entry into treated sites until spray has dried.

Incidental oral exposure (for example, hand-to-mouth exposure) from treated plants and outdoor household items is expected to be very minimal as denatonium benzoate is a bittering agent used to make harmful household chemicals less palatable for children.

The risk of exposure to denatonium benzoate for residential postapplication activities is not expected to be of concern due to the low toxicity of denatonium benzoate and low potential for exposure when label directions are followed.

3.3 Dietary Risk Assessment

There are no direct food or feed uses registered in the United States and Canada for denatonium benzoate.

Denatonium benzoate is one of the most bitter substances known, and most people are able to detect it at concentrations as low as 10 ppb; at 10 ppm, it is unpleasantly bitter. As such, it is added to a variety of household products (non-pesticidal uses) such as toiletries, liquid detergents and anti-freeze to deter accidental ingestion.

Considering the low concentration at which it is unpalatable, the registered non-food uses and low application rate of denatonium benzoate, dietary exposure from food and water is expected to be minimal. Water monitoring is not needed.

Dietary risk to denatonium benzoate is not expected to be of concern due to its low toxicity and low potential for dietary exposure.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

In Canada, denatonium benzoate is used as a repellent for deer and other wild and domestic animals. It is topically applied to leaves and stems via hand-held spray application.

Environmental fate data for denatonium benzoate are summarized in Table 1 of Appendix III. Denatonium benzoate is soluble in water (45.0 g a.i./L). Since it is an organic salt it is not expected to volatilize (vapour pressure $< 1 \times 10^{-7}$ mm Hg at 60°C). Abiotic transformation processes (phototransformation and hydrolysis) are not significant routes of transformation in aquatic and terrestrial environments. Denatonium benzoate is stable to phototransformation in soil (half life 235 days). In water, phototransformation half lives ranged from 15 days (pH 5) to stable (pH 9). Denatonium benzoate is stable to hydrolysis (half-life greater than one year at pH 4, 5, 7 and 9).

The octanol-water partition coefficient (K_{ow}) for denatonium benzoate is 0.91 which indicates that it is unlikely to bioaccumulate. There is no data on biotransformation half lives for denatonium benzoate in soil and aquatic environments. Biotransformation studies in soil and water are waived by PMRA, with the rationale of negligible potential exposure to the environment. There are no field studies indicating dissipation rates.

With respect to adsorption to soils, K_d values range from 527.9 to 7.9 mL/g (immobile to low mobility). Soil column leaching studies show that less than 0.05% of applied denatonium benzoate was detected in the leachate, indicating a strong affinity of denatonium benzoate to soil. Therefore, denatonium benzoate is not expected to leach significantly in soils.

The only transformation product is lignocaine obtained during hydrolysis at low pH. Its fate in the environment has not been fully characterized.

4.2 Environmental Risk Characterization

4.2.1 Risks To Terrestrial Organisms

Assessment of the risk of denatonium benzoate to terrestrial organisms was limited to birds because of a lack of available toxicity data for mammals and terrestrial invertebrates. A summary of terrestrial toxicity data for denatonium benzoate is presented in Table 2 of Appendix III. For the assessment of risk, toxicity endpoints chosen from the more sensitive of the two species tested in the laboratory were used as surrogates for the wide range of avian species that can be potentially exposed following treatment with denatonium benzoate.

The acute oral LD_{50} for the bobwhite is 196 mg a.i./kg bw. The subacute dietary LC_{50} for the bobwhite and the mallard is greater than 5200 mg a.i./kg diet and the NOEC is 5200 mg a.i./kg diet. Therefore, denatonium benzoate is classified as "moderately toxic" to birds via acute oral exposure and "practically non-toxic" to birds via dietary exposure. This is in accordance with the EU DAR[6] (August 2008) which concludes that, although denatonium benzoate is acutely toxic, "continuous ingestion of the product does not seem to have an impact on the [bird] species tested."

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6 EU DAR (August 2008): European Union Draft Assessment Report. This report was finalized on 8 October 2008 and was included in Annex I of Directive 91/414EEC of European Commission.

Since denatonium benzoate is applied to tree bark and leaves which are not food items for birds, and the application area is quite limited in extent (applied by a hand held sprayer), birds are not expected to be significantly exposed to food sources from applications of denatonium benzoate. Therefore, a quantitative risk assessment was not carried out for birds.

There is no data available on the effects of denatonium benzoate on terrestrial mammals. Given the fact that denatonium benzoate is applied to young sprouts of trees and has an aversion effect (bitter taste), the exposure to mammals is unlikely.

Plant toxicity studies conducted with denatonium benzoate or its transformation product were not available for review. However, as denatonium benzoate is a repellent to be used on plants, adverse effects to non-target terrestrial plants are not expected.

4.2.2 Effects on Aquatic Organisms

The aquatic risk assessment was based on an evaluation of toxicity data on denatonium benzoate for rainbow trout and one estuarine/marine species (mysid shrimp). No acceptable toxicity data were available for warm water fish species, daphnia and freshwater and marine plant or alga species and no toxicity data on the transformation products was available for aquatic studies. For the risk assessment, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with denatonium benzoate. The endpoints were derived by dividing the LC_{50} from the laboratory study by a factor of 10 for fish and 2 for mysid shrimp.

The data submitted by the registrant indicate that the 96-hr LC_{50} for estuarine/marine invertebrates (shrimp) is 400 mg/mL and the 96-hr LC_{50} for fish (rainbow trout) is greater than 1000 mg/mL.

The screening level risk assessment presented in Table 3 of Appendix III indicates that denatonium benzoate poses a negligible risk to freshwater fish, marine shrimp and amphibians. In addition, based on the use pattern, exposure to aquatic organisms is expected to be limited. The PMRA requires standard statements for avoiding drift and contamination of water supplies for all commercial product labels. Proposed label amendments are listed in Appendix II.

5.0 Pest Control Product Policy Considerations

5.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, denatonium benzoate was assessed in accordance with the PMRA Regulatory Directive DIR99-03[7] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Denatonium benzoate does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Table 1 of Appendix IV for comparison with Track 1 criteria.

Denatonium benzoate is not expected to form any transformation products that meet all Track 1 criteria.

5.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical are compared against the list in the *Canada Gazette*. The list is used as described in the PMRA Notice of Intent NOI2005-01[8], *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the New Pest Control Products Act and is based on existing policies and regulations including: Regulatory Directives DIR99-03 and DIR2006-02[9], and taking into consideration the Ozone-depleting Substance *Regulations*, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade denatonium benzoate does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*.

- The end-use products, Deer Guard, Tree Guard and Super Hunter, do not contain any formulants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

6.0 Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. There were no health-related incident reports submitted to the PMRA for end use products containing denatonium benzoate as of February 11, 2011.

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7 DIR99-03: *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.*

8 NOI2005-01: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

9 DIR2006-02: *Formulants Policy and Implementation Guidance Document.*

7.0 Organisation for Economic Co-operation and Development Status of Denatonium benzoate

Canada is part of the Organisation for Economic Co-operation and Development (OECD), which groups 30 member countries and provides governments with a setting in which to discuss, develop and perfect economic and social policies.

Based on the current available information, the use of denatonium benzoate as a repellent to deter deer from damaging deciduous and conifer trees in forests is accepted in the European Union (final EU Review Report October 2008). In the US, the registrant requested a voluntary cancellation of all denatonium benzoate products effective December 1, 2009 and the USEPA did not publish a re-registration eligibility decision for denatonium benzoate.

8.0 Summary

8.1 Human Health and Safety

The available database is considered sufficient to conclude that there is a very low level of concern for the hazard following exposure of animals to denatonium benzoate. The database indicates that denatonium benzoate is not genotoxic or carcinogenic. Denatonium benzoate has a history of use in various household products and meets the criteria established for non-conventional pesticides. Due to the considerations identified, a quantitative risk assessment is not required.

8.1.1 Occupational Risk

Occupational exposure to denatonium benzoate is expected to be minimal if the label directions are followed.

8.1.2 Dietary Risk from Food and Drinking Water

Dietary exposure to denatonium benzoate is expected to be negligible based on the registered use, low application rate, and bitterness of the compound.

8.1.3 Non-Occupational Risk

Non-occupational exposure to denatonium benzoate is expected to be minimal if the label directions are followed.

8.2 Environmental Risk

There are no biotransformation studies to assess the persistence of denatonium benzoate in soils and aquatic systems. However, the studies are waived by the PMRA, with the rationale of negligible potential exposure to the environment. Denatonium benzoate is not mobile and has a low potential to leach to groundwater. A screening level risk assessment indicates that it is not a

risk to freshwater fish, amphibians and estuarine/marine invertebrates. A screening risk assessment for birds was not required since denatonium benzoate is applied to tree bark and leaves which are not food items for birds, and the application area is quite limited in extent (applied by a hand held sprayer).

The PMRA risk assessment and available fate and toxicity data indicate that continued use is not likely to pose a significant risk to the environment and the method of application (hand held sprayer) limits the potential exposure to relatively small areas.

9.0 Proposed Regulatory Decision

The PMRA is proposing continued registration of products containing denatonium benzoate for sale and use in Canada with the implementation of additional mitigation measures on their labels. The labels of Canadian end-use product must be amended to include the label statements listed in Appendix II. A submission to implement label revisions will be required within 90 days of finalization of the re-evaluation decision. No additional data are being requested at this time.

List of Abbreviations

µg	microgram
ADI	acceptable daily intake
a.i.	active ingredient
aPAD	acute population adjusted dose
ARfD	acute reference dose
ARI	aggregate risk index
ARTF	Agricultural Re-entry Task Force
atm	atmosphere(s)
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetre(s)
cPAD	chronic population adjusted dose
cRfD	chronic reference dose
CSFII	Continuing Survey of Food Intakes by Individuals
DACO	data code
DEEM	Dietary Exposure Evaluation Model
DT_{50}	dissipation time to 50%
DWLOC	drinking water level of comparison
EDWC	estimated drinking water concentration
EEC	expected environmental concentration [also estimated environmental concentration]
EXAMS	Exposure Analysis Modeling System
FIRST	FQPA Index Reservoir Screening Tool
FQPA	*Food Quality Protection Act*
g	gram(s)
ha	hectare
IRED	Interim Reregistration Eligibility Decision
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)
LEACHM	Leaching Estimation and Chemistry Model
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
m	metre(s)
m^3	metre(s) cubed
mg	milligram(s)
mm	millimetre(s)

mm Hg	millimetre mercury
MOE	margin of exposure
MRL	maximum residue limit
nm	nanometre
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
PCPA	*Pest Control Products Act*
PDI	potential daily intake
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
PIC	Prior Informed Consent
p*K*a	-log10 acid dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PRVD	Proposed Re-evaluation Decision
PRZM	Pesticide Root Zone Model
Q_1*	cancer potency factor
RED	Reregistration Eligibility Decision
REI	restricted-entry interval
RfD	reference dose
RVD	Re-evaluation Decision
RQ	risk quotient
SCI-GROW	Screening Concentration in Ground Water
TC	transfer coefficient
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Registered Products Containing Denatonium Benzoate as of 3 June 2011

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (%)
25197	Technical	Macfarlan Smith Ltd.	Bitrex® Technical	granular	99.9
25199	Commercial	Becker Underwood, Inc.	Tree Guard® Commercial Deer Repellent suspension	suspension	0.20
29095	Commercial	Repel Holdings, Inc.	Deer Guard Commercial Deer Repellent	suspension	0.20
24456	Domestic	Superior Control Products Inc.	Super Hunter	solution	0.075
25198	Domestic	Becker Underwood, Inc.	Tree Guard® Deer Repellent	suspension	0.20
29078	Domestic	Repel Holdings, Inc.	Deer Guard Deer Repellent	suspension	0.20

Appendix II Label Amendments for Products Containing Denatonium Benzoate

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the above label statements.

A submission to request label revisions will be required within 90 days of finalization of the re-evaluation decision.

The labels of end-use products in Canada must be amended to include the following statements to further protect workers and the environment.

I) The following statement must be included in a section entitled **PRECAUTIONS**.

For Commercial and Domestic products:

For outdoor use only.

II) The following statements must be included in a section entitled **DIRECTIONS FOR USE**.

For Commercial products:

Avoid application of this product when winds are gusty.

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

DO NOT apply by field sprayer or by air.

DO NOT apply to fruit bearing trees.

Buffer zones:

Use of hand-held or backpack sprayers and spot treatments DO NOT require a buffer zone.

III) The following statements must be included in a section entitled **PRECAUTIONS**.

For Domestic product PCP# 24456 to standardize label statements:

Wear chemical resistant gloves when handling product or contaminated equipment.

Do not enter treated area until spray has dried.

Appendix III Environmental Assessment

Table 1 Fate and Behaviour of Denatonium Benzoate in the Environment

Study Type	Test Material	Study Conditions	Value or Endpoint	Interpretation	Major Transformation Products
Abiotic transformation					
Hydrolysis (25°C)	Denatonium benzoate	pH 5 (25°C) pH 7 (25°C) pH 9 (25°C)	DT_{50}: Stable Stable Stable	Not a major route of transformation at environmentally relevant pH	Lignocaine
Phototransformation soil	Denatonium benzoate	Sandy loam soil, OM of 1% and pH 6.9	DT_{50}: Stable	Not an important route of transformation	Not determined
Phototransformation water	Denatonium benzoate	pH 5 pH 7 pH 9 (after 30 days)	15 d (SFO) DT_{50}: 42.6 d (SFO) Stable (235 d)	A potential route of transformation in acidic environment (pH 5)	No determined
Biotransformation					
Soil - aerobic	Denatonium benzoate	N/A	N/A	N/A	N/A
Soil - anaerobic	Denatonium benzoate	N/A	N/A	N/A	N/A
Water/sediment - aerobic	Denatonium benzoate	N/A	N/A	N/A	N/A
Water/sediment-anaerobic	Denatonium benzoate	N/A	N/A	N/A	N/A
Mobility Adsorption/ desorption	Denatonium benzoate	pH % OM%sand Kitley stoke: 6.3 2.5 24.5 Easter Howgate: 4.9 1.4 28.9 Boghall: 4.5 9.5 42.7 Balmanno: 7.0 4.1 6.0	K_d: 7.9 mL/g 11.4 mL/g 20.8 mL/g 527.9 mL/g	Immobile to low mobility	Not determined
Field dissipation (Canadian studies)	Denatonium benzoate	N/A	N/A	N/A	N/A

Table 2 Toxicity of Denatonium Benzoate to Non-target Species

Organism	Study Type	Species	Test material	Endpoint	Toxicity Value	Effect
Terrestrial Species						
Invertebrate	Acute contact	Honey bee (*Apis mellifera*)	N/A	N/A	N/A	N/A
	Acute contact	Earthworm (*Eisenia foetida*)	N/A	N/A	N/A	N/A
Birds	Acute oral	Bobwhite quail (*Colinus virginianus*)	Technical	14-d LD_{50}	>196 mg a.c./kg bw	Mortality
	Acute dietary	Bobwhite quail (*Colinus virginianus*)		5-d LC_{50}	>5200 mg a.c./kg diet	Mortality
		Mallard duck (*Anas platyrhynchos*)		5-d LC_{50}	>5200 mg a.c./kg diet	Mortality
Mammals	Acute	N/A	N/A	N/A	N/A	N/A
	Subchronic dietary	N/A	N/A	N/A	N/A	N/A
	Chronic	N/A	N/A	N/A	N/A	N/A
Plants	Seedling emergence	N/A	N/A	N/A	N/A	N/A
	Vegetative vigor	N/A	N/A	N/A	N/A	N/A
Freshwater Organisms						
Invertebrates	Acute	N/A	N/A	N/A	N/A	N/A
	Chronic	N/A	N/A	N/A	N/A	N/A
Fish	Acute	Warm water fish	N/A	N/A	N/A	N/A
		Rainbow trout (*Oncorhynchus mykiss*)	Technical	96-h LC_{50}	>1000 mg a.c./L	Mortality
Amphibian	Chronic	Rainbow trout (*Oncorhynchus mykiss*) surrogate	Technical	96-h LC_{50}	>1000 mg a.c./L	Mortality
Algae	Acute	N/A	N/A	N/A	N/A	N/A
Vascular Plants	Acute	N/A	N/A	N/A	N/A	N/A

Organism	Study Type	Species	Test material	Endpoint	Toxicity Value	Effect
Terrestrial Species						
Marine Organisms						
Shrimp	Acute	Saltwater shrimp (*Mysidiopsis bahia*)	Technical	96-h LC_{50}	>400 mg a.e./L	Mortality
Fish	Acute	N/A	N/A	N/A	N/A	N/A
Algae	Acute	N/A	N/A	N/A	N/A	N/A
N/A = Not available						

Table 3 Screening Level Risk Assessment of Denatonium Benzoate to Aquatic Organisms

Organism (Species)	Exposure	Test substance	Endpoint value (mg a.e./L) ÷ safety factor*	EEC (mg a.e./L)**	RQ***
Freshwater species					
Cold fish: Rainbow trout *Onchorynchus mykiss*	Acute	TGAI	96-hour LC_{50} = 1000 ÷ 10 = 100 mg a.i./L	80 cm depth = 1.88	0.02
Amphibians (surrogate: Rainbow trout)	Acute	TGAI	96-hour LC_{50} = 1000 ÷ 10 = 100 mg a.i./L	15 cm depth = 6.33	0.05
Marine species					
Saltwater shrimp *Crangon sp.*	Acute	TGAI	96-hour LC_{50} > 400 ÷ 2 = 200 mg a.i./L	80 cm depth = 1.88	0.01

* Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.

** EEC b ** EEC based on a 15 cm water body depth for amphibians and an 80 cm water depth for all other aquatic organisms.

*** Values in bolt character have a RQ > 1

Appendix IV Toxic Substances Management Policy

Table 1 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria for Denatonium Benzoate

TSMP Track 1 Criteria	TSMP Track 1 Criterion Value		Denatonium benzoate Are criteria met?	Transformation Products Are criteria met?
CEPA toxic or CEPA toxic equivalent*	Yes		No	Not available
Predominantly anthropogenic**	Yes		No	Not available
Persistent	Persistent in one of the following media:		Persistent in Soil and water/sediment system.	Not available
	Soil	Half-life ≥ 182 days	Stable	Not available
	Water	Half-life ≥ 182 days	Not < pH 7	Lignocaine
	Sediment	Half-life ≥ 365 days	N/A	Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure ($< 1 \times 10^{-7}$ mm Hg at 60 °C)	Not available
Bioaccumulative	The log L_{OW} and/or BCF and/or BAF are preferred over log K_{OW}.		Not bioaccumulative	Not available
	Log $K_{ow} \geq 5$		-0.0041	Not available
	BCF ≥ 5000		N/A	Not available
	BAF ≥ 5000		N/A	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	Not expected to meet TSMP Track 1criteria.

* All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e. all other TSMP criteria are met).

** The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

References

Studies considered in the Chemistry Assessment

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

Unpublished Information

PMRA Document Number	Reference
1490725	Bitrex (Active Ingredient for Anipel Formulations) Part 2 of Data Submission - 2.12 to 2.15. Submitted July 20, 1992., DACO: 2.11,2.13.3 CBI
1490733	Bitrex (Active Ingredient for Anipel Formulations) Part 2 of Data Submission - Specifications and Analytical Methodology. Volume 3 of 8. Submitted July 20, 1992., DACO: 2.14 CBI
1490736	Bitrex (Active Ingredient for Anipel Formulations) Part 2 of Data Submission - Specifications and Analytical Methodology. Volume 3 of 9. Submitted July 20, 1992., DACO: 2.14 CBI
1491092	1995, Bitrex (denatonium benzoate): Determination of the Dissociation Constant., DACO: 2.14.10
1491095	1992, Denatonium Benzoate - n-octanol/Water Partition Coefficient., DACO: 2.14.11 CBI

Studies considered in the Health Risk Assessment

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

Unpublished Information

PMRA Document Number	Reference
1140947	DENATONIUM BENZOATE: ACUTE ORAL TOXICITY STUDIES IN RATS AND RABBITS (H-2281)(ANIPEL ML1 & ML2 TABLETS), DACO: 4.2.1
1140948	ASSESSMENT OF ACUTE DERMAL TOXICITY OF DENATONIUM BENZOATE TO RATS (12364)(ANIPEL ML1 & ML2 TABLETS), DACO: 4.2.2

1140949 DENATONIUM BENZOATE - ACUTE INHALATION TOXICITY STUDY IN RATS (636766)(ANIPEL ML1 & ML2)(3824), DACO: 4.2.3

1140950 EXPERIMENTS ON THE IRRITATING ACTION OF DENATONIUM BENZOATE ON THE OCULAR MUCOSA (TH-002/73)(ANIPEL ML1 & ML2 TABLETS), DACO: 4.2.4

1140951 A STUDY ON SAFETY OF DENATOMIUM BENZOATE FOR THE SKIN (TH-001/73)(ANIPEL ML1 & ML2 TABLETS), DACO: 4.2.5

1140952 REPORT ON SKIN SENSITISING POTENTIAL OF DENATONIUM BENZOATE IN GUINEA PIGS ((G11012;WPT/86/094)(ANIPEL ML1 & ML2 TABLETS), DACO: 4.2.6

1140954 CONTRACT FOR TESTING THE ACUTE AND CHRONIC TOXICITY OF DENTONIUM BENZOATE NF (BITREX) TWO YEAR ORAL STUDY IN RATS, REPORT, GOLDENTHAL ET AL, NOVEMBER 22, 1978 (H-2281;2F;366-006)(ANIPEL ML1 & ML2 TABLETS), DACO: 4.4.1

1140956 REPORT ON THE MICORBIAL MUTAGENICITY SCREEN ON DENATONIUM BENZOATE, REPORT, D.J. WEDD, D.G. GATEHOUSE, DECEMBER 1985 (WPT/85/216)(ANIPEL TABLETS ML1 & ML2), DACO: 4.5.4

1140957 MOUSE MICRONUCLEUS TEST WITH DENATONIUM BENZOATE, REPORT, J.C. JENSEN, SEPTEMBER 17, 1990 (12365) (ANIPEL TABLETS ML1 & ML2), DACO: 4.5.4

1490733 Bitrex (Active Ingredient for Anipel Formulations) Part 2 of Data Submission - Specifications and Analytical Methodology. Volume 3 of 8. Submitted July 20, 1992., DACO: 2.14 CBI

1491095 1992, Denatonium Benzoate - n-octanol/Water Partition Coefficient., DACO: 2.14.11 CBI

1866992 2010, Exposure Modeling, DACO: 5.2

Studies considered in the Environmental Risk Assessment

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

Unpublished Information

PMRA Document Number	Reference
1140944	SUMMARIES: BITREX (ANIPEL ML1 & ML2 TABLETS), DACO: 4.1
1140961	SUMMARIES: DENATONIUM BENZOATE (ANIPEL TABLETS ML1 & ML2), DACO: 8.1
1140962	DENATONIUM BENZOATE- N-OCTANOL/WATER PARTITION COEFFICIENT (PC-002/92)(ANIPEL TABLETS ML1 &ML2), DACO: 8.2.1
1140963	DENATONIUM BENZOATE PHOTOLYSIS IN AQUEOUS SOLUTION AND SOIL (SAC 92/001)(ANIPEL TABLETS ML1 & ML2), DACO: 8.2.1
1181143	EVALUATION OF LEACHING/DEGRADATION OF DENATONIUM BENZOATE (BITREX) IN SOIL COLUMNS. A.VINTEN & R.SPIERS. STUDY COMPLETED: 31 OCTOBER 1991. [ANIPEL TABLETS ML1/ML2;SUBN#92-0925,92-0926], DACO: 8.2.4.2,8.2.4.3.1
1181165	SUMMARIES: BITREX, DENATONIUM BENZOATE. [ANIPEL TABLETS ML1/ML2;SUBN#92-0925,92-0926;ENVIRONMENTAL TOXICOLOGY VOLUME 9 OF 9;SUBMITTED: 20 JULY 1992], DACO: 9.1
1181176	DENATONIUM BENZOATE-ACUTE ORAL TOXICITY (LD50) TO BOBWHITE QUAIL. B.HAKIN ET.AL. STUDY COMPLETED: JUNE 19,1992. (MCS5/920535). [ANIPEL TABLETS ML1/ML2;SUBN#92-0925,92-0926;ENVIRONMENTAL TOXICOLOGY VOLUME 9 OF 9;SUBMITTED: 20 JULY 1992], DACO: 9.6.2.1
1181205	EFFECT OF DENATONIUM BENZOATE ON THE MORTALITY RATE OF RAINBOW TROUT (SALMO GAIRDNERI). M.DOUGLAS & I.PELL. STUDY COMPLETED: AUGUST 1981 (STUDY PRE-DATES ABOVE GUIDELINE). (GUIDELINE 72-1;GXO52). [ANIPEL TABLETS ML1/ML2;SUBN#92-0925,92-0926;ENVIRONMENT
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1226671 1985, 8-DAY DIETARY LC50 STUDY WITH AC 263, 499 IN BOBWHITE QUAIL, DACO: 9.6.2.1

1226673 1985, 8-DAY DIETARY LC50 STUDY WITH AC 263, 499 IN MALLARD DUCKLINGS, DACO: 9.6.2.1

B. ADDITIONAL INFORMATION CONSIDERED

Published Information

Reference

European Commission, 2008, Draft Assessment Report (DAR) - Public Version - Initial Risk Assessment Provided by the Rapporteur Member State Portugal for the Existing Active Substance Dentonium Benzoate - Volume 1 - 3, DACO: 8.6,9

European Commission, 2008, Final Review Report for the Active Substance Dentonium Benzoate; Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 28 October 2008 in view of the inclusion of denathonium benzoate in Annex I of Directive 91/414/EEC.